

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Office**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/403,844 04/18/95 FODSTAD

O 7885.33USWO

EXAMINER

HM12/0228

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GABEL, G	
ART UNIT	PAPER NUMBER

1641

JX

DATE MAILED:

02/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/403,844	Fodstad et al.
Examiner Gailene R. Gabel	Group Art Unit 164

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

12-6-99

Responsive to communication(s) filed on _____.

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

Claim(s) 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, 64 is/are pending in the application.

Of the above claim(s) 66-67, 69, 71-72, 75, 78-79, 87-89, 92-93, is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, is/are rejected.

Claim(s) 64, 66-67, 69, 71-72, 75, 78-79, 87-89, is/are objected to.

Claim(s) 92-93, 96, 101, 105-107 are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on _____ is approved disapproved.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

Information Disclosure Statement(s), PTO-1449, Paper No(s). 25 Interview Summary, PTO-413

Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152

Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____

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DETAILED ACTION

Amendment Entry

1. Applicants' response filed 12/6/99 is acknowledged and has been entered. Currently, claims 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 78-79, 87-89, 92-93, 96, 101, and 105-107 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 22, 39, 48, and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 contains parenthetical symbols which renders the claim indefinite because it is unclear whether the limitations inside the parentheses are a part of the claimed invention. See MPEP § 2173.05(d). See also claim 71.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 22-25, 28, 29, 33, and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. (EP 016,552) in view of Connelly et al. (U.S. Patent 5,422,277) for reason of record.

4. Claims 22, 34-40, 43, 48, 67, 69, 71, 72, 75, 87-89, 92, 93, 96, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Kemmer et al. (Journal of Immunological Methods, 1992) and Holmes et al. (WO 91/09938) and in further view of Terasaki et al. (U.S. Patent 4,752,569) for reason of record. Examiner concurs that discussion of Holmes was inadvertently excluded in the previous Office Action in Paper No. 24. However, Holmes et al. was previously discussed in Paper No. 9.

5. Claims 22, 46-48, 51, 59-62, 64, 66, 67, 69, 71, 78, 79, 106, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Forrest et al. (U.S. Patent 4,659,678) for reason of record.

6. Claims 22-25, 28-29, 33-40, 43, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 78-79, 87-89, 92-93, 96, 101, and 105-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen (US 5,374,531) taken altogether with Hermentin et al. (US 5,095,097) or Ullman et al.

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(US 5,536,644). Please see Paper No. 14 of Application Serial Number 08/704,619 or Atty Docket Number 788541USWO for a thorough discussion of the references aforementioned.

In sum, Jensen teaches assaying for various particular analytes, e.g. human cells, using a pair of reagents, i.e. a detection reagent and a separation reagent (the instant labeled additional antibody and antibody coated paramagnetic particle, respectively). Typical assay conditions include adding sample and reagents, placing on a conventional plate shaker for five minutes at room temperature at a high speed to keep the reagent particles suspended while allowing for specific reagent particle-binding to the targeted cell population with minimal non-specific binding; followed by flow cytometric analysis. Optimum incubation times and temperatures are result effective variables and can be determined via routine experimentation. Pretreatment of a sample with a fixative is a conventional means of stabilizing cell membrane structures and providing access to intracellular antigens. Hermentin is incorporated herein for his teachings directed to (para)magnetic protein conjugates useful for specific removal of cells from solutions or body fluids and teaches that nonspecific adsorption onto paramagnetic particles can be prevented or reversed by addition of a suitable reagent (see Abstract and col. 4, lines 45-48). Alternatively, Ullman has been incorporated herein for his teachings drawn to (para)magnetic particle based separation methods and teaches the use of a "releasing agent" when particles are nonspecifically aggregated primarily through hydrophobic interactions. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods, reagents, kits of Jensen by adding a mild detergent as claimed to prevent or reverse nonspecific

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adsorption onto paramagnetic particles as taught by Hermentin et al. or to release nonspecifically aggregated particles as taught by Ullman et al. because one of ordinary skill in the art would have expected reduction of nonspecific binding and/or nonspecific aggregation of the particulate reagent to improve the sensitivity and specificity of the method of Jensen.

Double Patenting

7. Claims 22-23, 28-29, 33-40, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 79, 87-89, 92-93, 96, 101, and 105-107 are rejected under 35 U.S.C. 102(f) as being anticipated by Fodstat et al. (ASN 08/704,619).

Claims 22-23, 28-29, 33-40, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 79, 87-89, 92-93, 96, 101, and 105-107 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. Application Serial Number 08/704,619 contains claims that conflict with the instant invention. While Oystein Fodstad is a common inventor, both applications claiming identical subject matter appear to have different inventive entities.

8. Claims 22-23, 28-29, 33-40, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 79, 87-89, 92-93, 96, 101, and 105-107 are directed to the same invention as that of claims 19-24, 26-40, 44, 45, 47-72, 74-89, 93-109, and 118-122 of commonly assigned Application Serial Number 08/704,619. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

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Since the Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

9. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

10. Claims 22-23, 28-29, 33-40, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 79, 87-89, 92-93, 96, 101, and 105-107 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 19-24, 26-40, 44, 45, 47-72, 74-89, 93-109, and 118-122 of copending Application No. 08/704,619. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

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11. Claims 22-23, 28-29, 33-40, 46-48, 51, 59-62, 64, 66-67, 69, 71-72, 75, 79, 87-89, 92-93, 96, 101, and 105-107 provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 08/704,619 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Response to Arguments

12. A) Responsive to the rejection of claims 22-25, 28, 29, 33, and 105 as unpatentable over Widder et al. and Connelly et al., Applicants argue that prima facie case of obviousness has not been established as there is no reasonable expectation of success; the cited references do not teach or suggest all of the claim limitations and even if one of ordinary skill in the art were to combine or modify the references, he or she would not achieve the present invention. Applicants

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specifically argue that Widder discloses a method for coarse separation and not the detection of a target cell as submitted in previous communications to the Office. Applicants further argue that Connelly fails to cure deficiencies in the Widder reference and further differs from the instant invention because Connelly fixes killed, rather than live, target cells.

In response, Widder, indeed, teaches a method for separating target cells from a mixed cell population using magnetic particles coated with a layer of monoclonal antibodies that are specific to membrane structures for selectively binding to target cells. Widder also teaches that the magnetically responsive microspheres have Protein A associated into the surface which selectively binds antibodies through the Fc region of the antibodies so that Fab arms of the antibodies extend outwardly for binding. In Example 2, Widder separates and detects RBCs or target cells that were labeled with ^{51}Cr and bound to microspheres using a gamma counter. Connelly was incorporated therein for his teaching in polyethylene sorbitans monolaurate, a fixative composition for use in fixing internal components of target cells without destroying cellular properties. Specifically, Connelly teaches various fixatives for use in fixing cells without destroying cellular properties by incubating at decreased temperatures in column 9, lines 20-48. It would have been obvious to one of ordinary skill in the art to use antibodies to immobilize other specific antibodies on the surface of the magnetic particles in the method of Widder because such method of immobilizing highly specific antibodies on the surface of a solid support, such as magnetic particles is conventional and well known in the art. It would have been obvious to one of ordinary skill in the art to use detergents in specific concentrations to treat

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cells as used by Connelly following certain specific temperature and time parameters because the use detergents to treat cells is well known and conventional in the art for removing extraneous matter from the cells that will interfere with assays. One of ordinary skill in the art would have been motivated to incorporate Connelly's fixative techniques into Widder method because Connelly specifically states that one of ordinary skill in the art of cell fixation may routinely have to vary the aforementioned cell treatment parameters as in Widder's RBCs (dependent on cellular type) in order to obtain desired cell fixation without substantial destruction of cellular properties.

B) Applicants argue that use of protein A in the microspheres of Widder causes binding of target cells and non-target cells alike causing unacceptable reduction in specificity and the applicants successfully have overcome these disadvantages.

In response, protein A as used in Widder appears to advantageously, selectively, and specifically bind antibodies to target cells (supra). Furthermore, Widder incubated 0.5 mg of microspheres in suspension in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate) (see Example 1). The use of detergents is well known and conventional in the art for removing extraneous matter from the cells that will interfere with specificity in assays. In incorporating Connelly's incubation parameters within low temperature range which was proposed to vary between cells of interest, a required specificity as that of the instant invention can be achieved. While applicants continue to reiterate that their method

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overcomes alleged deficiencies in Widder reference in combination with Connelly, they fail to provide data to support such allegation and fail to disclose specific elements and kinetics in the instant invention which distinctly differentiates it from the Widder and Connelly references so as to effect increased level of specificity. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation of success in identifying target cells with a high degree of specificity using the combined methods of Widder and Connelly.

C) Responsive to the rejection of claims 22, 34-40, 43, 48, 67, 69, 71, 72, 75, 87-89, 92, 96, and 101 as unpatentable over Widder et al. in view of Kemmer et al. and Holmes et al. and in further view of Terasaki et al., Applicants argue that prima facie case of obviousness has not been established as there is no reasonable expectation of success; Kemmer, Holmes, and Terasaki do not cure the deficiencies of Widder, the combination of references do not teach or suggest all of the claim limitations and even if one of ordinary skill in the art were to combine or modify the references, he or she would not achieve the present invention.

In response, protein A as used in Widder appears to advantageously, selectively, and specifically bind antibodies to target cells (supra). Furthermore, Widder incubated 0.5 mg of microspheres in suspension in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate) (see Example 1). The use of detergents is well known and conventional in the art for removing extraneous matter from the cells that will interfere with specificity in assays. Kemmer was incorporated for his teaching in isolation of tumor cells from

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a mixed cell suspension of human tumor tissue which contains tumor cells, leucocytes, and erythrocytes, using magnetic beads coated with monoclonal antibodies. Holmes was incorporated for his teaching in separation of hematopoietic progenitor cells from a mixed population of hematopoietic cells which contain malignant cells using magnetic microbeads coated with sheep-anti mouse antibody which binds to the Fc portion of IgG mouse antibodies. Terasaki teaches incorporation of monoclonal antibodies labeled with enzyme such as horseradish peroxidase and conjugated with other antibodies or with magnetic particles in reagents for use in detection methods of neoplastic conditions. It would have been obvious to one of ordinary of ordinary skill in the art at the time of the instant invention to use the method of Widder to separate cells from a variety of cell samples such as taught by Kemmer, Holmes, and Terasaki because of the advantage of removing tumor cells from a mixed cell suspension using magnetic microbeads coated with monoclonal antibodies for studying the tumor cells and purging a sample of tumor cells and use of various monoclonal antibodies specific for neoplastic cell lines such as those taught by Terasaki is well known for detection of target antigens so that a skilled artisan would have had a reasonable expectation of success in choosing specific monoclonal antibodies specific for surface antigens to identify target cells in any cell population of interest with the level of specificity such as claimed by the instant invention when combined with Widder reference. While applicants continue to reiterate that their method overcomes alleged deficiencies in Widder reference, they fail to provide data to support such allegation and fail to disclose specific elements and kinetics in the instant invention which distinctly

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differentiates it from the Widder reference in combination with other references so as to effect increased level of specificity. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation of success in identifying target cells with a high degree of specificity using the combined methods of Widder, Kemmer, Holmes, and Terasaki.

D) Responsive to the rejection of claims 22, 46-48, 51, 59-62, 64, 66, 67, 69, 71, 78, 79, 106, and 107 as unpatentable over Widder et al. in view Forrest et al., Applicants argue that prima facie case of obviousness has not been established as there is no reasonable expectation of success Forrest does not cure the deficiencies of Widder, the combination of references do not teach or suggest all of the claim limitations and even if one of ordinary skill in the art were to combine or modify the references, he or she would not achieve the present invention.

In response, protein A as used in Widder appears to advantageously, selectively, and specifically bind antibodies to target cells (supra). Furthermore, Widder incubated 0.5 mg of microspheres in suspension in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate) (see Example 1). The use of detergents is well known and conventional in the art for removing extraneous matter from the cells that will interfere with specificity in assays. Forrest was incorporated in his teaching of a sandwich assay wherein a complex is formed between antigen in a sample and two or more antibody reagents and bound to paramagnetic particles having labeled or unlabeled antibodies attached thereto. It would have been obvious to one of ordinary skill in the art to use a binding system such as avidin-biotin as

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taught by Forrest et al. in the method of Widder et al. because Forrest et al. teach that avidin-biotin provides a very rapid and high binding affinity which offers the advantage of a speed, accuracy, and specificity in an assay.

13. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

14. Applicants comments and arguments were considered but not persuasive. Therefore, no claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The

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examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel 2/25/00

Gailene R. Gabel
Patent Examiner
Art Unit 1641

James C. Housel 2/26/00

JAMES C. HOUSEL
ADVISORY PATENT EXAMINER